Amendments

Claims 1-15 were canceled without prejudice or disclaimer as being directed to a non-elected invention. Specifically, in the Office Action of October 23, 2001 (paper no. 11), Claims 1-15 were restricted from Claims 19-28. In their response, Applicants elected, without traverse, to prosecute the invention of Claims 19-28. By this amendment, non-elected Claims 1-15 are canceled without prejudice or disclaimer. Applicants reserve the right to file a divisional application directed to this non-elected invention.

A copy of pending claims 19-28 is attached hereto for the convenience of the Examiner.

Rejection under 35 U.S.C. § 103(a)

Claims 19-28, all of the claims remaining in this application, remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bolton 5,591,457 (the '457 patent), Bolton 5,834,030 (the '030 patent), or Tremblay 6,136,308 (the '308 patent) "in view of applicant's admission of what is known in the art at page 6, first full paragraph of the specification." Office Action of February 19, 2003 at page 2. Specifically, the Office Action alleged that:

> "Since the instant specification at page 6 teaches that "*neurological disorders are associated with increases in apoptosis* is known" [sic] . . . and since the references are treating *such physical traumas or neurological diseases* with the *same process* as that which is claimed then it would have been obvious to perform a method for alleviating or protecting against the symptoms of a neurological medical disorder involving accelerated rates of apoptosis or necrosis in a mammalian body by performing the method of the references . . . [emphasis added].

Applicants have addressed this rejection in the Reply of October 17, 2002. In this Response, Applicants asserted, *inter alia*, that the cited references simply cannot be combined to support a *prima facie* case for obviousness. Of the three cited patents, only the '030 patent

contains any reference to neurological disorders, specifically, *nitric oxide associated neurological disorders*, such as depression. And none of the cited references disclose the treatment of apoptosis-associated disorders.

Since these argument are of record, Applicants will not reiterate the arguments herein. However, Applicants specifically note that the statement "it is noted that applicant never addresses the fact that Bolton '030 does in fact mention that the claimed method can be used to treat neurological disorders" (Office Action of February 17, 2003 at page 3) is inaccurate. Applicants addressed this issue at the middle of page 5 of the Reply of October 17, 2002, further noting that the '030 patent contains a reference only to *nitric oxide associated neurological disorders*.

In response to the maintained rejection under 35 U.S.C. § 103(a), Applicants submit herewith a Declaration under 37 C.F.R. § 1.132, authored by Dr. Stanley Appel, Professor and Chairman of the Department of Neurology at Baylor College of Medicine. Dr. Appel's Declaration makes clear that depression, as disclosed in Bolton '030 isn not associated with apoptosis by experts in the field. This Declaration further substantiates the underlying pathology of both Alzheimer's disease and Parkinson's disease and differentiates their pathology with increased nitric oxide production as cited in the '030 patent. This Declaration concludes that based on their pathology, "[a] process taught to increase the production of nitric oxide would be regarded as totally inappropriate for treatment of neurodegenerative diseases.

Based on the facts presented in Dr. Appel's Declaration and the arguments already of record in this application, Applicant's submit that there is no legal basis for maintaining the outstanding obvious rejection under the standard set forth in *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Furthermore, there is no scientific basis, in view of what is known about depression and what is known about the neurological disorders recited in claim

19, for concluding that the cited reference could be combined to render the instant invention obvious.

For at least these reasons, the outstanding obvious rejection must be withdrawn.

New rejection under 35 U.S.C. § 112, first paragraph

Claims 19-28 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter not described in the specification in such a way as to enable one skilled in the art . . . to make and/or use the invention." Office Action of February 19, 2003 at pages 3-4.

The legal standard for enablement is whether one of ordinary skill in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). *Wands* identifies a number of factors to be considered in determining whether a disclosure is enabling for the full scope of the claims, *i.e.*, (i) the breadth of the claims, (ii) the nature of the invention, (iii) the state of the prior art, (iv) the level of one of ordinary skill, (v) the level of predictability in the art, (vi) the amount of direction provided by the inventor, (vii) the existence of working examples, and (viii) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *Id.*

In issuing the new enablement rejection, the Office Action appears to focus on an alleged lack of direction (support) provided by the specification and the alleged unpredictability in the art (*i.e.*, above elements (v) and (iv), respectively).

Applicants first traverse the rejection based on the alleged lack of support provided in the specification. The instant Specification at pages 8-12 describes in detail how treat an aliquot of a mammal's blood with temperature stress (see, *e.g.*, page 9, line 22 - page 10, line

8), oxidative stress (see, *e.g.*, page 10, lines 9-24), and/or ultraviolet light stress (see, *e.g.*, page 10, line 25 - page 11, line 12). The Specification describes the length of time for which the blood should be stressed (see, *e.g.*, page 11, lines 13-21), the time course for treatment (see, *e.g.*, page 12, lines 4-9), and an apparatus useful for exposing a blood aliquot to all three stresses in the same container (see, *e.g.*, page 11, line 22 - page 12, line 3). In addition to these indicated portions of the Specification, the Examples at pages 12-18 provide exemplary regimens for treating a variety of mammals.

Based on the instant Specification, a practitioner has ample guidance to treat a mammal's blood with stressors and reintroduce the blood to the mammal. Applicants fail to understand the basis for an enablement rejection based on this aspect of the disclosure.

With respect to unpredictability in the art, Applicants submit that the Office Action has improperly focused the enablement inquiry on the admitted etiological complexity of many of the diseases recited in pending claim 19. While these individual apoptosis-associated neurological diseases may indeed be biologically complex, the autologous blood stressing method of claim 19 can be practiced without a thorough understanding of the underlying neurological diseases. It is sufficient for the practitioner to understand that the diseases are associated with apoptosis and that the claimed invention reduces apoptosis. In this respect, the actual process of using the claimed invention is fundamentally the same regardless of the apoptosis-associated neurological disease being treated. Thus while the different neurological diseases recited in claim 19 may indeed be complex, the nature of the invention is such that practicing the invention is not adversely affected by this complexity.

Accordingly, when viewed in light of the nature of the invention, the state of the prior art, the level of one of ordinary skill, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the

invention based on the content of the disclosure (*i.e.*, Wands factors (ii), (iii), (iv), (vi), (vii), and (viii), above), one skilled in the art would have to conclude that the Specification is fully enabling for the full scope of the claimed invention. Whatever unpredictability there may be in the field of apoptosis-associated neurological disorders has little bearing on practicing the instant invention. Upon reading the instant Specification, a practitioner could readily stress an aliquot of mammal's blood and reintroduce the stressed blood to reduce apoptosis and treat apoptosis-associated neurological disorders. Accordingly, the Specification is fully enabling for the full scope of the claimed invention.

For at least these reasons, Applicants submit that the enablement rejection is improper ans should be withdrawn.

CONCLUSION

Applicant submit that the present application is now fully in condition for allowance. Early notification to that effect is earnestly requested.

Respectfully submitted,

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CONFORMED COPY OF THE PENDING CLAIMS

19. A method for alleviating or protecting against the symptoms of a neurological medical disorder involving accelerated rates of apoptosis or necrosis in a mammalian body, which method comprises (a) selecting a patient having or suspected of having a neurological medical disorder selected from the group consisting of Parkinsons's disease, senile dementia and Alzheimer's disease; (b) reacting an aliquot of blood from the mammalian body *ex vivo* with at least one stressor selected from the group consisting of a temperature above or below body temperature, ultraviolet light and an oxidative environment; and (c) administering the aliquot of blood treated in step (b) to the mammalian body; thereby reducing the rate of or susceptibility to apoptosis or necrosis of tissues and organs.

20. The method of claim 19 wherein the aliquot of blood has a volume from about 0.1-100 ml.

21. The method of claim 20 wherein said at least one stressor is a temperature in the range from about -5° to 55° C.

22. The method of claim 20 wherein said at least one stressor is a temperature in the range of from about 40° to 50°C.

23. The method of claim 20 wherein said at least ones stressor is an oxidative environment comprising a mixture of ozone and medical grade oxygen, bubbled through the blood aliquot.

24. The method of claim 23 wherein the gaseous mixture has an ozone content of from about 100-100 μg per ml.

25. The method of claim 20 wherein said at least one stressor is ultraviolet light in the UV-C band wavelength.

26. The method of claim 20 wherein all three said stressors are applied to the aliquot simultaneously.

27. The method of claim 26 wherein said stressors are applied for a period of time from 0.5 to 60 minutes.

28. The method of claim 27 wherein the time is from about 2 to 5 minutes.